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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/529,748	03/30/2005	Berislav V Zlokovic	GRT/4061-32	1588

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EXAMINER	
KOLKER, DANIEL E	
ART UNIT	**PAPER NUMBER**
1649	
MAIL DATE	**DELIVERY MODE**
10/15/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/529,748	ZLOKOVIC ET AL.	
	Examiner	Art Unit	
	Daniel Kolker	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 August 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18,22 and 23* is/are pending in the application.

4a) Of the above claim(s) *1-5,22 and 23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *6-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-18,22 and 23* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/27/05; 8/30/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *See Continuation Sheet*.

Continuation of Attachment(s) 6). Other: Email message indicating publication date of Society for Neuroscience Abstracts.

DETAILED ACTION

1. The remarks filed 30 August 2007 have been entered. Claims 1 – 18 and 22 – 23 are pending.

Election/Restrictions

2. Applicant's election with traverse of Group II (claims 6 – 18) in the reply filed on 30 August 2007 is acknowledged. The traversal is on the ground(s) that the lack of showing that examining all three groups together would constitute a serious burden on the examiner. This is not found persuasive because contrary to applicant's assertion, examination of all three groups together would in fact constitute a serious burden. Group II requires search and consideration of the step of administration, which is not required for consideration of Group I. Group III requires search and consideration for the library of candidate agents as well as the step of selecting an agent by its ability to inhibit apoptosis, neither of which is required for consideration of group I or II. There are different issues for examination posed by the different groups, including both prior art and non-prior-art issues (e.g. different enablement and written description issues with respect to 35 USC 112, first paragraph). Separate search and consideration would be required for each group. Thus, there would be a serious burden on the examiner if all three groups were to be examined together.

The requirement is still deemed proper and is therefore made FINAL.

3. Claims 1 – 5 and 22 – 23 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 30 August 2007.

4. Claims 6 – 18 are under examination.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 6 – 18 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for administration of protein S, does not reasonably provide enablement for administration of "a functional variant thereof" as recited in claim 6 or for the

variants with particular activities as recited in claims 8 – 11 and 17 – 18. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

There are many factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue. These factors include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (FED. Cir. 1988).

Here, the nature of the invention is complex, as it is drawn to protecting cells within a subject's nervous system by administering either a protein or a functional variant of a protein. Protecting cells such as neurons from damage which has not yet occurred is a complex endeavor, as the health of cells depends on multiple factors, including DNA damage, the degree of cellular activation by neurotransmitters such as glutamate, continued supply of nutrients from the bloodstream, as well as external factors such as blunt trauma.

Protein S is a large glycoprotein, comprising over 600 amino acids (specification, p. 12 lines 20 – 25). The examiner concedes that the protein itself is well-known in the art; see for example Bouma (U.S. Patent 5,663,142, issued 2 September 1997, cited on IDS filed 27 April 2005), particularly Figure 5 as well as column 1 lines 15 – 26 which discuss the structure and refer to published references that describe the structure in more detail. However, the specification fails to provide sufficient guidance or working examples to the skilled artisan to enable him to make and use the full scope of the variants recited in the claims. Although the claims are drawn to methods, discussion here is on point to the products, which are required as starting materials for the methods.

At pp. 13 – 14, the specification discusses certain mutations to protein S. It is within the skill of the artisan to make such mutations. However, the specification does not disclose whether or not those mutations result in a "functional variant" of protein S, as recited in claim 6. The specification fails to disclose which mutations, changes, deletions, or insertions to protein S sequences impart the properties recited in claims 8 – 11 and 17 – 18. There are no working examples of functional variants which have the appropriate properties; the only examples are of protein S itself. The specification fails to show any correlation between structures within protein

S and the various properties. Thus the artisan would have to discover, on his or her own, those structures which are necessary and sufficient to impart the functional variants of protein S with the requisite properties.

In the absence of a great deal of experimentation it would be very difficult to determine which regions of protein S, which is a very large protein, are required for the protein to be a "functional variant" or for the protein to have the particular properties recited in claims 8 – 11 and 17 – 18. Rudinger states on page 3 that "it is impossible to attach a unique significance to any residue in a [protein] sequence. A given amino acid will not by any means have the same significance in different peptide sequences, or even in different positions of the same sequence". Rudinger further states on page 6 that "the significance of particular amino acid sequences for different aspects of biological activity cannot be predicted *a priori* but must be determined from case to case by painstaking experimental study". While technical improvements in methods of making mutant proteins have developed since 1976 when Rudinger was published, the basic thrust of the article, and the particular passages cited, has not in fact changed. Inferring protein shape and function from amino acid sequence changes remains a very difficult problem that is full of unpredictability. See the attached article by Honig (October 1999. Journal of Molecular Biology 293:283-293). Note that Honig teaches that despite technical progress since he began studying the problem of protein folding in 1970, considerable work remains to be done to be able to predict a protein's shape, and therefore its structure, once an amino acid sequence is known. See p. 289 – 290 for a discussion of the problems and challenges that remain in this field.

Thus in order to determine how to make the claimed functional derivatives as claimed, the artisan would have to resort to painstaking experimentation. Given the breadth of the claims and the lack of guidance commensurate with their very broad scope, the degree of experimentation required would be undue.

6. Claims 6 – 18 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

Independent claim 6 encompasses administration of "at least one functional variant" of protein S. Dependent claims 8 – 11 and 17 – 18 recite certain properties of the protein S or functional variant thereof which are administered. The specification fails to describe which variants have the stated properties, and fails to disclose which parts of the protein S sequence are either necessary or sufficient for the resultant variant to retain the appropriate property. The skilled artisan could not immediately visualize which variants are to be administered in the claimed methods, because the specification, claims, and drawings fail to indicate which structural features of protein S are common to all variants, and which features are common to all variants with the various functions recited in dependent claims 8 – 11 and 17 – 18.

The instant disclosure of protein S does not adequately support the scope of the claimed genus, which encompasses a substantial variety of subgenera and can be of any structure at all. A genus claim may be supported by a representative number of species as set forth in *Regents of the University of California v Eli Lilly & Co,* 119F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997), which states:

"To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention". Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (1997); In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1980) ("[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed.") Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." Lockwood, 107 F.3d 1565, 1572, 41 USPQ2d at 1966.

An adequate written description of a DNA, "requires a precise definition, such as by structure, formula, chemical name, or physical properties," not a mere wish or plan for obtaining the claimed chemical invention. Fiers v. Revel, 984 F.2d 1164, 1171, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993). Accordingly, "an adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself." Id at 1170, 25 USPQ2d at 1606." While the above quotations from Fiers are on point to DNA, the same logic applies to proteins, which are required as starting materials for the claimed methods.

Claim Rejections - 35 USC § 102

7. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 6 – 18 are rejected under 35 U.S.C. 102(a) as being anticipated by Cheng (2002. Society for Neuroscience Abstract 390.13, cited on IDS filed 27 April 2005).

The enclosed email message from the USPTO's library indicates the reference was available as a CD-ROM on 19 August 2002, which is prior to the date that provisional application 60/414333 was filed. While the meeting at which the abstract was presented was later, the reference itself was printed prior to the filing date and therefore qualifies as prior art under 35 USC 102(a).

Cheng teaches administration of protein S is sufficient to protect neurons within the brain from damage. The reference teaches every element of claim 6. Human protein S was used, anticipating claim 7. It is reasonable that the protein S administered by Cheng has anti-thrombotic and anti-inflammatory activity, as recited in claims 8 – 9. Cheng teaches that protein S has "significant neuroprotective" effects, as recited in claim 10. Cheng teaches protein S exerts its effects through the Ax1 tyrosine kinase receptor, as recited in claim 11. Claim 12 is anticipated as no protein C is administered. Claim 13 is anticipated as the mice are not disclosed as having any protein S deficiency. Claim 14 is anticipated as the reference by Cheng teaches administration after ischemia, which causes hypoxia, and subsequent re-oxygenation. Claim 15 is anticipated as the mice from Cheng are clearly at risk of hypoxia, owing to the damage to the middle cerebral artery. Claim 16 is anticipated as the protein is administered before diagnosis of any other condition. Claim 17 is rejected as Cheng teaches

that protein S increases cerebral blood flow. Claim 18 is rejected as the reference teaches that the volume of the infarct and brain edema are reduced following administration of protein S.

8. Claims 6 – 13 and 15 – 17 are rejected under 35 U.S.C. 102(b) as being anticipated by Schwarz (U.S. Patent 5,254,532, issued 19 October 1993).

Claim 6 as written does not require that the patient have any particular disease or disorder; the claim encompasses prophylactic administration to protect neurons from future damage. Likewise, claim 15 clearly indicates that the subjects to be administered the protein S (or variant) are "at risk for injury" caused by certain conditions, but does not require that the subject be suffering from these conditions.

Schwarz teaches administration of pharmaceutical compositions comprising protein S to patients (rabbits) prior to receiving an injection of the thrombogenic substance FEIBA; see column 5 lines 1 – 28. As the rabbits are about to receive a thromogenic substance, they are at risk of injury caused by ischemia, hypoxia, re-oxygenation injury, or a combination thereof, as recited in claim 15 and encompassed by claim 6. While the patent is silent with respect to neuroprotection, this will necessarily happen upon administration of protein S. Thus the patent by Schwartz anticipates claim 6.

Claim 7 is anticipated as Schwarz teaches using human protein S (see column 2 line 30 – column 3 line 7; column 3 lines 47 – 59; column 4 lines 35 – 62). It is reasonable that the protein S administered by Schwartz has anti-thrombotic and anti-inflammatory activity, as recited in claims 8 – 9, since it is disclosed in the patent (column 5 lines 22 – 27) to be effective in preventing thrombosis. Claims 10 – 11 are rejected as they recite certain properties which are inherent to protein S. Claim 12 is rejected as no protein C is administed. See column 5 lines 18 – 28; see also claims 1 and 3 of the Schwartz patent which clearly indicate that addition of protein C is optional. Claim 13 is rejected as the rabbits used were normal and not disclosed as having any particular protein S deficiency (column 4 final paragraph). Claim 16 is anticipated as the protein S is administered prior to diagnosis of disease and prior to administration of the thrombogenic agent. Claim 17 is rejected as the cerebral blood flow will increase upon administration of the agent.

9. Claims 6 and 8 – 18 are rejected under 35 U.S.C. 102(e) as being anticipated by Hung (U.S. Patent Application Publication 2003/0060415, published 27 March 2003, filed 2 October

2002, claiming benefit of earlier-filed applications from 1 November 1996 and 1 November 1995).

Hung teaches administration of compositions comprising protein S for treatment and prevention of of many conditions including ischemia and reperfusion injury, which are recited in claims 14 – 15 and encompassed by claim 6. See Hung, paragraph [0011] and [0019] – [0039] for diseases to be treated or prevented; see also paragraph [0041] as well as claims 1 and 48 which specifically list protein S as an agent to be administered for such treatment. As the reference teaches administration of a composition comprising protein S to patients in need of neuroprotection, the reference anticipates claim 6.

Claims 8 – 11 are rejected as the protein S necessarily has those properties recited; a chemical compound and its properties are inseparable. Claim 12 is rejected as protein C and activated protein C are not required to be administered by the reference; their inclusion is optional and listed as one of several alternatives. Claim 13 is rejected as the subjects to be treated are not disclosed as having protein S deficiency. Claims 14 – 15 are rejected as the particular patient populations in those claims are explicitly recited in paragraphs [0011] and [0019] – [0039] of the reference and because the reference teaches both prevention (i.e. administration before the disease or condition) and treatment (administration after the disease or condition). Claim 16 is rejected as the treatment is to occur prior to some future diagnosis of any other disease or condition. Claim 17 is rejected as the cerebral blood flow will increase upon administration of the agent. Claim 18 is rejected as the disease which are to be treated, including ischemia and thrombosis, will result in brain injury, infarction, or edema and therefore will be ameliorated by the administration of protein S.

Double Patenting

10. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re*

Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 6 – 11 and 13 – 18 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 – 6 of U.S. Patent No. 7,074,402. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant claims (with the exception of claim 12, which is not subject to this rejection) encompass administering both protein S and activated protein C for protection from neuronal cell death; claims 1 – 6 of the '402 patent encompass administration of activated protein C and protein S for protection from neuronal cell death and for reducing neuronal inflammation. While the reference is not by another and therefore does not serve as prior art under 35 USC 102(e), the issued '402 claims would anticipate the instant claims.

Conclusion

11. No claim is allowed.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel Kolker whose telephone number is (571) 272-3181. The examiner can normally be reached on Mon - Fri 8:30AM - 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Patent Examiner
Daniel E. Kolker, Ph.D.
October 3, 2007

Kolker, Daniel E.

From: Hensle, Kristine (ASRC)
Sent: Tuesday, October 02, 2007 1:59 PM
To: Kolker, Daniel E.
Subject: Pubdate for SfN, 32 Annual Meeting abstracts

Examiner Kolker,

Re: Cheng et al. 2002. Society for Neuroscience Abstracts, 32nd Annual Meeting, Abstract No. 390. 13

The meeting abstracts were first available August 19, 2002 (cd-rom). (Abstracts were posted online August 27, 2002. Meeting dates were Nov. 2-7, 2002.)

Kristine Hensle

Librarian

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